

Physician approaches to beta-lactam use in patients with penicillin hypersensitivity

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ABSTRACT

Beta-lactam antibiotics are widely used, but hypersensitivity reactions are common and difficult to manage. This study was designed to identify lack of knowledge regarding the safe use of alternative beta-lactams in penicillin-allergic patients and assess management differences between allergists and nonallergists. An electronic physician survey was sent to 623 providers in allergy, internal medicine, pediatrics, and family medicine, querying beta-lactam use in patients with a history of penicillin allergy. A total of 110 (17.7%) surveys were completed. For patients with a prior maculopapular rash to penicillin, most providers were uncomfortable prescribing penicillins again, although they would use other beta-lactams. In patients with an exfoliative dermatitis to penicillin, 46% of responders would not prescribe any beta-lactam again. For patients with a positive skin test to penicillin, only 45.1% of nonallergists were comfortable prescribing monobactams versus 62.5% of allergists; 30.3% of all responders would give a carbapenem. In patients with urticaria to penicillin, pediatricians were the most comfortable prescribing third- or fourth-generation cephalosporins. Providers (both allergists and nonallergists) were unfamiliar with the safety of prescribing penicillin in patients with history of maculopapular rash, the safety of monobactams, and low cross-reactivity with carbapenems in penicillin-allergic individuals. Nonallergists were also unfamiliar with the usefulness of penicillin skin testing. Improved education is needed to address these areas. Additionally, we found variability in responses regarding exfoliative dermatitis and comfort prescribing cephalosporins in patients with suspected IgE-mediated drug allergy to penicillin, highlighting the need for additional research in these areas.

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The β -lactam antibiotics are widely used as first-line agents in outpatient and inpatient clinical settings. Hypersensitivity to β -lactams, particularly penicillin, is a common problem, with up to 10–15% of patients reporting a history of penicillin allergy.^{1,2} Hypersensitivity reactions are complex and may be driven by different mechanisms, including IgE, complement, immune complexes, and T cells. Even within these mechanistic classes, severity of reactions may represent a spectrum. For instance, T-cell-mediated reactions can range from benign maculopapular rashes to life-threatening toxic epidermal necrolysis (TEN). The complexity of the reactions alone makes drug allergy difficult to diagnose, manage, and research.

Previous physician surveys have highlighted the difficulty of managing penicillin allergy.^{3,4} Solensky *et al.* assessed physician management of infectious diseases

of varying severity in patients with penicillin allergy and showed a tendency of providers to choose broad-spectrum antibiotics such as vancomycin.⁴ Puchner and Zacharisen illustrated much variability in prescribing cephalosporins to patients with a variety of different reactions to penicillin.³ In part, some of these differences in practice may be because of a conflicting body of literature, because the true rate of cross-reactivity between members of the β -lactam family, particularly penicillins and cephalosporins, appears to be much lower than historically feared. This has resulted in confusion in the proper management of β -lactam allergy and differing recommendations from professional organizations.^{1,5} Consequently, for many patients with a history of penicillin hypersensitivity, the most common approach is avoidance of other β -lactams in favor of other drugs that may have broader spectrum of action and higher cost.^{2,6,7} Use of these alternative antibiotics may increase the risk of developing drug-resistant organisms, could result in less efficacious therapy, and might increase the rate of adverse outcomes.

Despite the complexities of penicillin allergy, the literature does support some definitive conclusions about proper management. For example, skin testing with a penicillin conjugate (penicilloyl-polylysine) and native penicillin G is a sensitive method of diagnosing IgE-mediated allergy (negative predictive value of $\geq 95\%$), and combining this with an oral

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challenge to penicillins essentially allows allergists to rule out allergy.^{1,8} This approach is used in our institution. In penicillin-allergic patients, multiple studies have shown that there is virtually no cross-reactivity between penicillins and monobactams,^{1,9} and relatively little (<1%) cross-reactivity between penicillins and carbapenems.^{10–12} Finally, data support that the presence of a delayed maculopapular rash with administration of amoxicillin/ampicillin (*i.e.*, nonmucosal rash that occurs after a week of antibiotic use) is not an IgE-mediated process and is not associated with a risk of life-threatening immediate reactions to penicillin.^{1,13}

We have observed that physicians at our institution tend to avoid β -lactams in patients with a history of penicillin hypersensitivity, despite cases where it may be appropriate to use these agents. As such, we designed a survey to assess how physicians currently manage patients with a history of penicillin allergy, with the intention to specifically analyze differences between allergists and primary care providers. Our ultimate goal was to identify lack of knowledge of the current evidence regarding use of penicillin skin testing and safe use of alternative β -lactams in putative penicillin-allergic patients and to identify areas where additional education and research are needed. Our findings and their significance are discussed in this study.

METHODS

After Institutional Review Board approval, an electronic survey was sent to 623 physicians and extended physician providers in allergy (16), internal medicine (234), pediatrics (219), medicine-pediatrics (26), and family medicine (128), at our institution. Providers were questioned about β -lactam use in patients with a history of a variety of different reactions to penicillin. These included maculopapular reactions, severe exfoliative dermatitis, and reactions consistent with an IgE-mediated mechanism. For each question, providers were asked to select other members of the β -lactam family that they would be comfortable prescribing, if any. Additionally, space was left for providers to free text comments if they wanted to offer additional explanation of their preferences (Table 1).

RESULTS

One hundred ten providers (17.7%) completed the entire survey. The number of responders in each specialty was as follows: internal medicine, 32 (29.1%); pediatrics, 46 (41.8%); medicine-pediatrics, 9 (8.2%); family practice, 7 (6.4%); allergy, 16 (14.5%; Fig. 1). Responders constituted different levels of training, with 64 (58.2%) attending physicians, 12 (10.9%) fel-

Table 1 Survey questions and answers

Clinical scenarios

In a patient with a history of maculopapular rash to penicillin

In a patient with a history of urticaria to penicillin

In a patient with a history of anaphylaxis (two or more of the following: hives/swelling, abdominal cramping/vomiting, bronchospasm, hypotension, and/or laryngeal edema) to penicillin

In a patient with a positive skin test confirming IgE allergy to penicillin

In a patient with a history of an exfoliative dermatitis reaction (SJS or TEN) to penicillin

For each of the clinical scenarios, would you feel comfortable prescribing

Penicillin

Amoxicillin

Carbapenem (*e.g.* imipenem and meropenem)

Monobactam (*e.g.* aztreonam)

First-generation cephalosporin

Second-generation cephalosporin

Third-generation cephalosporin

Fourth-generation cephalosporin

All of the above

Would need further testing

None of the above

Other: (please describe)

Providers were questioned about their comfort with prescribing β -lactams given several different clinical scenarios. Answer choices for each question were the same and providers were instructed to "select all that apply." If "other" was chosen, providers were prompted to type their answer into a provided space.

SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis.

lows, 31 (28.2%) residents, and 3 (2.7%) nurse practitioners.

Maculopapular Rash

We sought to assess physician comfort in prescribing penicillin or another β -lactam in a patient with a history of a maculopapular rash to penicillin. Allergists were more comfortable prescribing penicillin again (25%) as opposed to nonallergists (9.7%). A larger number were comfortable prescribing amoxicillin to these patients: 37.5 and 15% of allergists and nonallergists, respectively. Overall, the majority were not comfortable prescribing either penicillin or amoxicillin. Although most providers were more comfortable prescribing other β -lactams, there was still a small number (2.7%) who indicated that they would not feel comfortable prescribing any β -lactam antibiotic again and 5.5% indicated that they would need additional testing (Table 2).

Figure 1. Demographics of survey responders. (A) Distribution of responders by medical specialty. (B) Number of responders versus surveys sent within each specialty. Med-Peds = medicine/pediatrics.

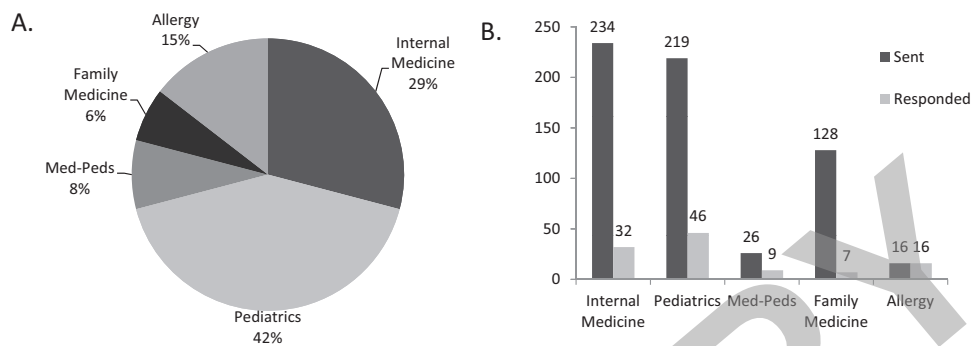


Table 2 Physician comfort in prescribing β -lactams in a patient with a history of a maculopapular rash

Answer Options	Response (%)	Response Count
Penicillin	11.8	13
Amoxicillin	18.1	20
Carbapenem	61.8	68
Monobactam	67.2	74
First-generation cephalosporin	68.1	75
Second-generation cephalosporin	73.6	81
Third-generation cephalosporin	80.0	88
Fourth-generation cephalosporin	75.5	83
Would need further testing	5.5	6
None of the above	2.7	3
Other	2.7	3

Exfoliative Dermatitis

When questioned about their use of β -lactams in patients with a history of severe exfoliative dermatitis (Stevens-Johnson syndrome or TEN); almost one-half of responders (46%) would not be comfortable with repeat use of this class of medications. No one was comfortable prescribing penicillin or amoxicillin again. Overall, the number of responders comfortable giving any other β -lactam was low, with the exception of monobactams, where 28.4% of responders indicated comfort with this medication. Twenty percent of responders indicated that they would request additional testing in patients with this history, but none indicated what type of testing they thought would be appropriate (Fig. 2). There was no appreciable difference in the answers to this question across specialties.

IgE-Mediated Reactions

In a patient with a history of urticaria to penicillin, we found that pediatricians were the most comfort-

able prescribing cephalosporins, particularly third-generation cephalosporins (64.6%), whereas allergists were the most likely to request additional testing first (Fig. 3).

In our survey, the majority of responders, both allergists and nonallergists, were not comfortable prescribing a carbapenem to a patient with a positive penicillin skin test: 12.5% of allergists and 15% of nonallergists would require additional testing; 30% of responders were comfortable prescribing a carbapenem without additional assessment. In contrast, most allergists (62.5%) were comfortable prescribing a monobactam in this patient population, while less than one-half (45.1%) of nonallergists indicated the same comfort.

All providers, including allergists, were more comfortable prescribing another β -lactam antibiotic (cephalosporin, carbapenem, or monobactam) when the patient had a history of positive skin test to penicillin versus a history of anaphylaxis (Table 3). Multiple providers wrote in responses indicating that they were not familiar with the use of or indications for penicillin skin testing.

DISCUSSION

β -Lactam antibiotics remain the first-line agents for a large number of infections, but their use is complicated by a high rate of allergy. Management of β -lactam allergy is challenging, complicated by knowledge gaps in the medical literature. However, there are definitive guidelines and evidence for testing and use of alternative agents in certain aspects of penicillin hypersensitivity. Our survey indicated that many clinicians are unfamiliar with these areas and identified points where additional education would be beneficial. These findings are discussed here.

A delayed maculopapular rash to penicillins is a common occurrence in clinical practice. These rashes typically occur about a week into the treatment course and are not associated with additional symptoms such as mucosal lesions, fever, or other systemic features. They may arise from T-cell-mediated reactions to the precipitating drug, or may even be caused by instead an underlying viral infection (*i.e.*, a rash that occurs

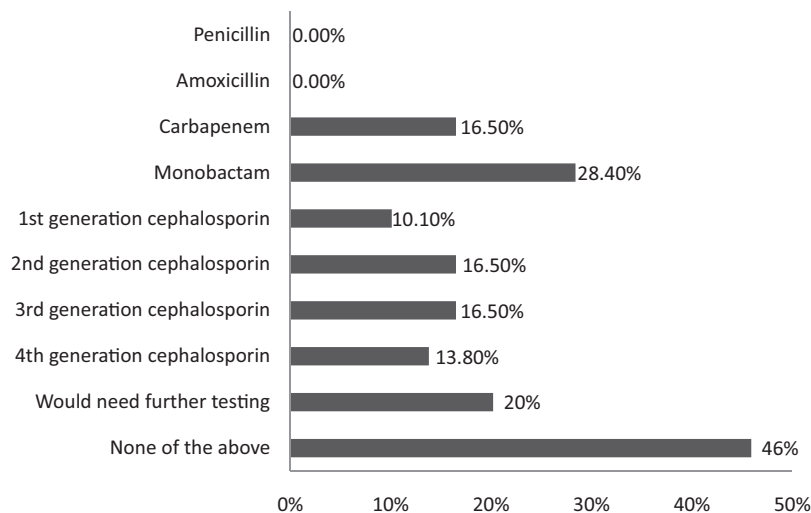


Figure 2. Percent of providers comfortable prescribing β -lactams in a patient with a history of severe exfoliative dermatitis to penicillin.

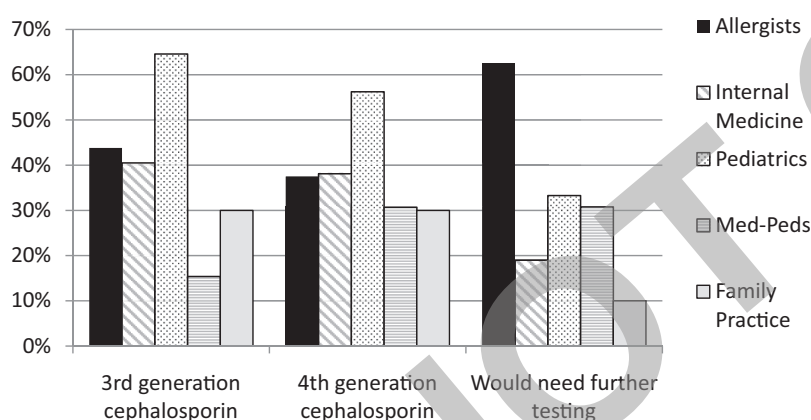


Figure 3. Percent of providers, by specialty, who would feel comfortable prescribing third- or fourth-generation cephalosporins in a patient with a history of urticaria to penicillin.

Table 3 Provider comfort in prescribing β -lactams in a patient with a history consistent with IgE-mediated allergy

Answer Options	Urticaria, Responses (%)	Anaphylaxis History, Response (%)	Positive SPT, Response (%)
Penicillin	0	0	0
Amoxicillin	1.8	0	0
Carbapenem	46.8	22.9	30.3
Monobactam	56	38.5	47.7
First-generation cephalosporin	37.6	5.5	22.9
Second-generation cephalosporin	45.9	9.2	29.4
Third-generation cephalosporin	52.3	10.1	37.6
Fourth-generation cephalosporin	49.5	9.2	33
Would need further testing	22.9	40.4	15.6
None of the above	9.2	24.8	18.3
Other	3.7	3.7	7.3

SPT = skin-prick testing.

when amoxicillin is administered during Epstein-Barr virus infection).¹⁴ In these cases, readministration of the offending antibiotic is usually not associated with any adverse effects.¹³ However, in our survey results, only a small number of providers were comfortable prescribing penicillin or amoxicillin in a patient with a

history of maculopapular rash. This suggests that use of β -lactams in these situations is underused.

IgE-mediated reactions to penicillins, on the other hand, carry significant risk for a severe reaction if the offending agent is readministered. These reactions arise from generation of IgE antibodies to penicillin-

protein complexes during a sensitizing course of the antibiotics. Future exposure results in an immediate hypersensitivity reaction that can include hives, bronchospasm, cardiovascular collapse, laryngeal edema, and/or gastrointestinal symptoms.

Fortunately, diagnostic skin testing with a combination of penicilloyl-polylysine and penicillin G provides high sensitivity and negative predictive values.⁸ When a negative skin test is followed by a negative oral challenge, IgE-mediated allergy to penicillin can be ruled out, and β -lactams can be safely used.^{1,15} Although we offer these services at our institution, our results indicated that many physicians are unfamiliar with this testing. Surprisingly, all providers were more comfortable prescribing a β -lactam in a patient with a positive skin test over a history of anaphylaxis. A positive skin test confirms the presence of an IgE-mediated allergy, so we expected that an equal or lower number of physicians would use a β -lactam in this case. Furthermore, ~80% of patients with a history of confirmed penicillin allergy will lose the sensitivity over a period of years,^{16,17} reinforcing the clinical importance of skin testing in the diagnosis of penicillin allergy.

In cases of suspected IgE-mediated allergy and in confirmed allergy (based on skin testing), many physicians (including allergists) were unaware of the safety of monobactam use. The safety of monobactams for patients with a history of IgE-mediated penicillin allergy has been well described in multiple studies.^{1,9} Based on these studies, there is virtually no risk for cross-reactivity between monobactams and penicillin; therefore, monobactams are safe to administer to patients with IgE-mediated penicillin allergy.^{1,9}

Although prior studies proposed that the rate of cross-reactivity between penicillin and carbapenems was high,¹⁸ newer prospective studies indicate that the true risk for cross-reactivity is <1%.^{10–12} Thus, current recommendations are that for individuals with confirmed IgE-mediated penicillin allergy, carbapenems can be given *via* graded challenge.^{1,10–12} In our survey, there was no appreciable difference between allergists' and nonallergists' responses; only a small number of providers were comfortable giving a carbapenem (30%) or performing further testing (15%). Because a graded challenge was not a specific answer choice, either of these answers could be interpreted as such, meaning that less than one-half of the responders were familiar with this option.

An area of confusion is the cross-reactivity between penicillin and cephalosporins. Although the rate of cross-reactivity was falsely elevated before 1980 because of the contamination of cephalosporins with penicillin,¹⁹ the true risk still remains unclear. There are several reasons for this. One, only a few prospective studies have sought to evaluate this question,^{19–27} and

given differing methodologies and the use of different cephalosporins in the studies, comprehensive statements are difficult to make. Two, a popular way of discussing cross-reactivity is based on cephalosporin generation; however, multiple studies have implied that side chains may be more important.^{28–32} Structurally, the side chains do not always correlate with a specific generation, making it difficult to assign broad generation-directed recommendations. Thus, professional organizations have made different recommendations for managing patients with penicillin allergy. The American Academy of Pediatrics supports the use of selected second- and third-generation cephalosporins with different side chains than penicillin (cefuroxime, cefpodoxime, and cefdinir) for penicillin-allergic patients without a history of life-threatening allergic reactions.^{5,33,34} In contrast, although the Joint Council of Allergy, Asthma, and Immunology also states that most hypersensitivity reactions to cephalosporins are directed at side chains rather than the β -lactam core, their current recommendations differ and promote a more conservative approach. These guidelines recommend avoidance, graded challenge (with or without cephalosporin skin testing), or desensitization to cephalosporins for patients who are proven to be penicillin allergic with a positive skin test.¹ This is likely the reason why, in our survey, pediatricians were more comfortable prescribing a third-generation cephalosporin to a patient with a history of urticaria to penicillin. However, because there are differing guidelines on this subject, it is not surprising that this is an area of confusion across specialties. Clearly, this is an area where focused, prospective, multicenter studies are needed to address the true rates of penicillin–cephalosporin cross-reactivity and determine which agents can be safely tolerated.

Finally, in terms of exfoliative dermatitis (Stevens-Johnson Syndrome or TEN), little is known about the potential for cross-reactivity. These are severe, non-IgE, immunologic reactions that are characterized by mucosal lesions, severe skin rashes with bullae and exfoliation, and multiple organ failure. Although it is widely accepted that the offending drug (and its immediate class) should be avoided,^{1,5} it is less clear if other members of that family of drugs are safe. In our survey, we found that about one-half of the providers would avoid the entire β -lactam family of medications in a patient with a severe exfoliative dermatitis reaction to penicillin. Twenty percent of responders would try to pursue additional testing, but, unfortunately, no testing currently exists for this type of reaction. It is also clear that some providers were comfortable prescribing certain members of the β -lactam family, with almost one-third of responders comfortable prescribing meropenem. At this time, there is no good evidence

to support any one approach, and, clearly, additional research in this area is necessary.

Our study does have limitations. Because this was a survey-based study, providers might not have honestly reflected their true clinical practice. Additionally, because our study was only distributed to providers at our institution and had a relatively low response rate (17.7%), a bias for how drug allergy is managed at our institution may be present. However, the number of responders to our survey is similar to previously published studies,⁴ and our survey was completed by a sampling of providers (mostly attending physicians) in pediatrics, internal medicine, and family practice, so the responses should still represent a variety of prior training experiences.

CONCLUSION

Penicillin allergy is a common and complicated problem. Avoidance of β -lactams can lead to the use of more expensive agents with broader spectrum of action adding to concerns about increasing microbial resistance, cost, and adverse outcomes. In our study, the majority of physicians were unfamiliar with the safety of prescribing penicillin in patients with history of maculopapular rash. Additionally, most providers lacked knowledge about the absolute safety of monobactams and the relative safety of carbapenems in penicillin-allergic individuals. Improved education, both for allergists and nonallergists, is needed to address these areas. In addition, many physicians are unaware of the usefulness of penicillin skin testing, and this is another area where increased education would be valuable. Allergists should take an active role in teaching pediatricians, internists, and family practitioners regarding the usefulness of penicillin skin testing and implications of the results, because these providers are typically the first to see these patients and will have an active role in referring appropriate patients.

The variability in responses pertaining to the cross-reactivity between penicillins and cephalosporins in IgE-mediated allergy and in patients with a history of exfoliative dermatitis further indicates the need for additional research and improved guidelines. It is of central importance that drug allergy education and research be better addressed. By giving providers the correct information and adequate tools for managing their patients with penicillin allergy, both the quality and the cost of care could be improved.

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